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Declaration under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS TO MINIMIZE LOSS THROUGH ADHESION TO EQUIPMENT SURFACES

(57) Abstract: The invention relates to a new process for preparing combination formulations of inhaled glucocorticoids and beta 2-agonists, e.g. budesonide in combination with formoterol. The process aims at minimizing adhesion of one or more of the ingredients to equipment surfaces by adding the ingredients to a container in a stepwise manner.

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Process to minimize loss through adhesion to equipment surfaces

The present invention relates to a new process for the preparation of combinations of drugs, in particular combinations of inhaled corticosteroids and β_2 agonists.

It is known that some pharmaceutical compounds suitable for administration via pressurised metered dose inhalers (pMDI's) have a tendency to adhere to the container surface. This problem is particularly noticeable with HFA formulations and there are patent applications, which detail the problem and possible solutions. For example, EP642992, WO96/32099 and US6253762 deal with adhesion on the walls of the MDI canister, but the term container used above is not limited to only the canister.

Less well known is that fact that the problem also applies to the surfaces of the manufacturing vessel and filling equipment. This makes filling of the metered dose inhaler container and subsequent dosing from those containers, less uniform. The problem has traditionally been overcome by adding an overage to the formulation, i.e. adding more of one or more of the ingredients than is theoretically required. However the effect cannot always be consistent enough for the overage method to alleviate the problem and as the extent of adhesion is not constant from batch to batch, much validation work has to be carried out to define the range of permitted overage for that product which will most likely result in an acceptable product in terms of reliable and consistent drug content for each dose. Details of such an investigation can be found in the proceedings of *Drug delivery to the Lungs 1997 pgs47-50 "Production Scale Optimisation of the Manufacturing Process for a HFA 134A Metered Dose Inhaler Containing Both Salmeterol and Fluticasone Propionate" Duquemin et al.* One of the parameters to be optimised was the drug overage I.e the amount of extra drug added to compensate for the loss of drug during the production process.

In the case of expensive drug compound, drug overages can add significantly to the cost of the final product. Also this is not nessessarily an easy solution as each active has to be optimised in combination products and the adhesion as mentioned above can vary from vessel to vessel and batch to batch. This can result in unacceptable rate of batch failure on dose content from the MDIs produced

Another factor is that the permitted overages are limited by the regulatory bodies to less than 10% of actives, which for a dilute product in a large production vessel may not be enough to cover losses.

It was found that if the actives were added to the mix in a predetermined and precise stepwise manner, one active added first in preference to the other, then no overages were necessary. This is a significant and suprising finding.

It would be assumed that as part of the mixing process, over time, the adhesion of each drug would be in proportion to a) its content in the mix and b) the area of the vessel. This has not turned out to be the case as no overage is required even in a large production vessel.

The first aspect of the invention therefore provides a process to minimise loss of one or more of the components through adhesion to equipment surfaces, which comprises addition of two or more components to a container in a stepwise manner in order to minimise loss of one or more of the components through adhesion to equipment surfaces.

The invention also provides a process for adding components to a multicomponent pharmaceutical formulation for inhalation comprising a step wise addition of the components to a container in order to minimize or iradicate losses due to adhesion of component to the container surface. The term "container" means any vessel suitable such as a glass or metal vessel used for the preparation of a pharmaceutical formulation such as pilot plant vessels and larger vessels used for pharmaceutical manufacture.

This invention particularly applies to formulations where the drug or drugs have a tendency to adhere to the surfaces of the manufacturing equipment in which they are mixed and through which they are dispensed into the container, canister or dosing device.

Also this invention particularly applies to the manufacture of suspension formulations and most preferably to that of drug suspended in a hydrofluoroalkane propellant. Preferred propellants are HFA 134a and HFA 227 and mixtures thereof.

The methodology of the production is known in the art and comprises the usual manufacturing equipment for preparation of large quantities of suspension formulation under pressure, for through-the-valve pressure filling of the canisters. However the principal could equally apply to equipment of smaller surface area and/or sytems not under pressure, for instance when MDIs are produced under the method of cold fill or where aqueous suspension formulations are being prepared.

Preferably the drugs of the invention are budesonide and formoterol or a hydrate of a salt thereof, in particular formoterol fumarate dihydrate.

Essentially, the larger component is added first. Essentially, therefore, the budesonide is added prior to the addition of the formoterol fumarate dihydrate.

The process of controlled addition significantly reduces the Formoterol normally lost during manufacture such that the manufacturing overages are significantly reduced, or preferably, not required at all.

Suitably the molar ratio of the budesonide to the formoterol fumarate dihydrate is from 2500:1 to 1:1.

The molar ratio of the budesonide to the formoterol fumarate dihydrate is preferably from 555:1 to 1:1, and more preferably from 150:1 to 1:1. The molar ratio of the budesonide to the formoterol fumarate dihydrate is even more preferably from 133:1 to 6:1. The molar ratio of the budesonide to the formoterol fumarate dihydrate is most preferably 50:1 to 6:1

In terms of dosing ratios for a combination product producted by this method, ratios in weight/weight terms are: Budesonide to Formoterol of 200:1 to 1:1, or more preferably 40:1 to 10:1.

In a further aspect the invention provides a pharmaceutical formulation prepared according to the above process and the use of such a formulation in therapy in particular the treatment and prophylaxis of respiratory disorders such as asthma and COPD.

The invention also provides a method of treating asthma or COPD, which comprised administering to a patient in need of such treatment a formulation as defined and prepared above.

The formulations prepared according to the invention optionally comprise one or more pharmaceutically acceptable suspending agents, valve lubricants, flavourings, bulking agents, sweetners or cosolvents. The formulations are preferably in the form of a micronised powder for inhalation suspended in a hydrofluoroalkane propellant, wherein

the particles of the pharmaceutically active ingredients have a mass median diameter of less than 10 μm.

EXPERIMENTAL DETAILS

The invention is illustrated by the following examples.

The examples shown below in Table 1 are of nine batches produced at a commercial manufacturing site

The amount of the active ingredients in the resulting pMDI's was assayed and compared to theoretical. The resulting API (active pharmaceutical ingredient) concentration was determined by Total Can Assay. The differences seen cannot be attributed to error in assay results due to analytical variation (Assay RSD 0.9%)

The results for each batch show the overage of Formoterol added, the theoretical amount expected if no loss occurs, the resulting assay figure and which API was added first.

TABLE 1

Batch	% Overage FFD	Order of Addition	Theoretical FFD % w/w	Actual FFD % w/w found on assay	% Difference between theoretical and actual	Mean of test results %
1	4.3	FFD 1st	0.0073	0.0071	2.7 %	
2	4.3	FFD 1st	0.0073	0.0070	4.1 %	
3	0	FFD 1st	0.0069	0.0067	2.9 %	3.23
4	3.4	BUD 1st	0.0072	0.0071	1.4 %	
5	0	BUD 1st	0.0069	0.0068	1.4 %	
6	0	BUD 1st	0.0069	0.0067	2.9 %	
7	0	BUD 1st	0.0069	0.0068	1.4 %	
8	0	BUD 1st	0.0069	0.0067	2.9 %	
9	0	BUD 1st	0.0069	0.0068	1.4 %	1.9

FFD = Formoterol fumurate dihydrate BUD = budesonide

Conclusion

The addition of Budesonide prior to the addition of Formoterol

1 reduces the amount of Formoterol that is lost during manufacture

2 such that the manufacturing overages are significantly reduced or negated entirely

3 gives advantage over random addition in that this method makes the outcome of the final API concentration more consistent and well within manufacturing allowances (+/- 5%)

4 reduces the likelihood of batch failure

5 thereby reducing overall costs.

Claims

1. A process to minimise loss of one or more of the components through adhesion to equipment surfaces, which comprises addition of two or more components to a container in a stepwise manner.

2. A process for adding components to a multicomponent pharmaceutical formulation for inhalation comprising a step wise addition of the components to a container in order to minimize or iradicate losses due to adhesion of component to the container surface.

3. A process according to claim 1 or 2 in which the component of largest mass is added first.

4. A process according to claim 2 or 3 in which the formulation components are active drug substances.

5. A process according to any one of claims 2 to 4 in which the formulation is for a pressurized metered dose inhaler.

6. A process according to claim 4 or 5 in which the active drug substances are budesonide and formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

7. A process according to any one of claims 4 to 6 in which the active drug substances are budesonide and formoterol fumarate dihydrate.

8. A process according to claim 7 in which the molar ratio of the budesonide to the formoterol fumarate dihydrate is from 2500:1 to 1:1.

9. A pharmaceutical formulation prepared according to the process defined in any one of claims 2 to 8.

10. A formulation according to claim 9 which is in the form of a suspension.

11. A formulation according to claim 10 in which the drugs are suspended in one or more HFA propellants.

12. A formulation according to claim 11 in which the HFA propellants are HFA 134a or HFA 227 or a mixture thereof.

13. Use of a formulation according to any one of claims 9 to 12 for the treatment or prophylaxis of asthma or COPD.

14. A method of treating asthma or COPD which comprised administering to a patient in need of such treatment a formulation according to any one of claims 9 to 12.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/001760

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/575, A61K 31/167, A61K 9/72, A61J 3/00, A61P 11/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI DATA, EPO-INTERNAL, PAJ, CADATA, EMBASE, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6004537 A (FRANK E. BLONDINO ET AL), 21 December 1999 (21.12.1999), column 1, line 38 - line 46; column 4, line 35 - line 47, tables 1-2	1-14
X	WO 0178737 A1 (GLAXO GROUP LIMITED), 25 October 2001 (25.10.2001), examples 1-2	1-14
X	US 5972919 A (CHRISTER CARL GUSTAV CARLING ET AL), 26 October 1999 (26.10.1999), column 4, line 1 - line 22, example 2	1-14

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 February 2004	10 -02- 2004
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Ingrid Eklund/ELY Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/001760

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9311773 A1 (AKTIEBOLAGET ASTRA), 24 June 1993 (24.06.1993), page 7, line 6 - line 28, example 2	1-14
X	WO 0053188 A1 (ASTRAZENECA AB), 14 Sept 2000 (14.09.2000), page 6, line 15 - line 22, examples 7-9	1-14
X	WO 0203958 A1 (ASTRAZENECA AB), 17 January 2002 (17.01.2002), examples	1-14

1.
Claims 13-14 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

2.
Present claims 1-12 relate to an extremely large number of possible processes/formulations. Support within the meaning of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the processes/formulations claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

The expression "addition /.../ in a stepwise manner" is not explained in a satisfactory way; it is not evident whether the different substances that are added separately, or whether a mixture of substances is added a little at a time. The expression "minimize loss /.../ through adhesion" is not further unfolded. Therefore, the claims also lack clarity (Article 5 and 6 PCT). An attempt is made to define the process/formulation by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, that is the process according to claim 6, with the following assumptions:

1. The process/formulation relates to a composition for inhalation of a combination of at least two active components, preferably formoterol fumarate dihydrate and budesonide, where the composition is a suspension that is to be administered in a pMDI.

2. One active component is added before the other.

3. The process implies that adhesion to the equipment of the active component added last is minimized.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/001760

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13-14
because they relate to subject matter not required to be searched by this Authority, namely:
see extra sheet

2. ☒ Claims Nos.: 1-12, partly
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see extra sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT
Information on patent family members

24/12/2003

International application No.
PCT/SE 2003/001760

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